Jinrong Bai[a], Yunsen Zhang[b], Ce Tang[b,c], Ya Hou[a], Xiaopeng Ai[a], Xiaorui Chen[a], Yi Zhang[b,c,d], Xiaobo Wang[b,c,*], Xianli Meng[b,c,*]

[a] College of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, 611137, China
[b] Innovative Institute of Chinese Medicine and Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, 611137, China [c] Ethnic Medicine Academic Heritage Innovation Research Center, Chengdu University of Traditional Chinese Medicine, Chengdu, 611137, China
[d] NMPA Key Laboratory for Quality Evaluation of Traditional Chinese Medicine (Traditional Chinese Patent Medicine), Chengdu University of Traditional Chinese
Medicine, Chengdu, 611137, China

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ABSTRACT

Gallic acid (GA), also known as 3,4,5-trihydroxybenzoic acid, is a natural secondary metabolite and widely isolated from various fruits, plants and nuts. In recent years, GA has received increasing attention for its powerful anti-inflammatory properties. The purpose of this review is to clearly illuminate the pharmacological activities and related molecular mechanisms of GA in inflammatory diseases. After consulting a large number of literatures, we made a comprehensive exposition on the chemical characteristics, plant origins, pharmacokinetics and toxicity of GA, especially its pharmacological activities and mechanisms of action. Although the plant source of GA is very rich, its lower extraction rate limits the application of GA in development. It is worth mentioning that GA can not only be separated from many plants, but also be produced in large quantities through biological and chemical synthesis. According to pharmacokinetic studies, the absorption and elimination of GA after oral administration are fast, while the structural optimization or dosage form adjustment of GA is beneficial to increase its bioavailability. Promisingly, toxicity studies have shown that GA scarcely has obvious toxicity or side effects in a variety of animal experiments and clinical trials. The results show that the anti-inflammatory mechanisms of GA mainly involved MAPK and NF-κB signaling pathways. It thus weakens the inflammatory response by reducing the release of inflammatory cytokines, chemokines, adhesion molecule and cell infiltration. Due to its excellent pharmacological activities, GA is expected to be a potential candidate for the treatment of various inflammation-related diseases. This paper will provide theoretical basis for the clinical application of GA and guide the future research and medicinal development of GA.

1. Introduction

Gallic acid (GA), a class of phenolic compounds, also known as 3,4,5- trihydroxybenzoic acid, is a naturally occurring secondary metabolite found in various plants, vegetables, nuts and fruits [1–3]. Among many polyphenols, GA is a low molecular weight tri-phenolic compound with excellent anti-inflammatory and anti-oxidative activities [4]. In addition, GA also has several evident pharmacological effects including anti-tumor, anti-bacterial, anti-diabetes, anti-obesity, anti-microbial and anti-myocardial ischemia [5–10]. Inflammation is a defensive reaction of multiple physiological and pathological processes to exert protective mechanisms against external stimulation and tissue damage [11]. Chronic or acute inflammation was demonstrated to stimulate the release of inflammatory mediators such as interleukin-1β (IL-1β), tumor

Abbreviation: cAMP, cyclic adenosine monophosphate; COX-2, cyclooxygenase 2; GA, gallic acid; IκBs, inhibitory proteins of NF-κB; ICAM-1, intercellular adhesion molecule 1; IFN-γ, interferon gamma; IgE, immunoglobulin E; IκKs, IκB kinases; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MKK, MAPK kinase; MKKK, MAPK kinase kinase; MMPs, matrix metalloproteinases; MyD88, myeloid differentiation primary response gene 88; NO, nitric oxide; NF-κB, nuclear factor kappa B; PGE2, prostaglandin E2; STAT-3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor beta; TIMP-1, inhibitor of metalloproteinases 1; TNF-α, tumor necrosis factor alpha.

* Corresponding authors at: Innovative Institute of Chinese Medicine and Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, 611137, China.
E-mail addresses: 1461875871@qq.com (X. Wang), xlm999@cdutcm.edu.cn (X. Meng).

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Table 1

V

various sources of GA.

No.	Plant species	Family	Used part	Drying	Extract	Amount isolated (mg/g)	Refs.
1	*Pueraria lobata* (Wild.) Ohwi	Leguminosae	Root	-	75 % Ethanol; Ultrasonic and soak	0.09	[42]
2	*Guazuma ulmifolia* Lam.	Malvaceae	Fruit	Lyophilizing	Methanol-acetone-water (7:7:6); Ultrasonic	0.0149	[43]
3	*Sambucus nigra* L.	Adoxaceae	Fruit	Lyophilizing	50 % Methanol containing 0.1 % formic acid; Ultrasonic	0.00345	[44]
4	*Syzygium malaccense* (L.) Merr. & L.M. Perry	Myrtaceae	Fruit peels	Lyophilizing	Anhydrous ethanol; Soak	0.002	[45]
5	*Sorocea guilleminina* Gaudich.	Moraceae	Leaves	Stoving	Boiling water; Soak	0.038	[46]
6	*Abutilon pannosum* (G.Forst.) Schltdl.	Malvaceae	Stem Bark	Air	Methanol; Soak	0.001	[47]
7	*Barringtonia racemosa* (L.) Spreng	Lecythidaceae	Leaves Stem	Lyophilizing Air Lyophilizing Air	Water; Soak	0.453 0.727 0.278 0.480	[48]
8	*Phyllanthus amarus* Schum. & Thonn.	Euphorbiaceae	Leaves	Air	Water; Soak	135.08	[49]
9	*Momordica charantia* L.	Cucurbitaceae				97.35	
10	*Fraxinus angustifolia* Vahl	Oleaceae	Bark	-	Water; Soak	0.00412	[50]
11	*Camellia japonica* L.	Theaceae	Seeds	Air	80 % Methanol and hexane, successively; Soak	0.64	[51]
12	*Myrciaria dubia* (Kunth) Mc Vaugh	Myrtaceae	Fruits	Stoving	40.7 % Water, 16 % Ethanol and 43.3 % propanone; Soak	4.732	[52]
13	*Antidesma bunius* Spreng.	Phyllanthaceae	Fruits	-	95 % Ethanol; Soak	0.26	[53]
14	*Mentha spicata* L.	Lamiaceae	Aerial parts	Air	Water; Soak	0.165	[54]
15	*Bougainvillea* Comm. ex Juss.	Nyctaginaceae	Flowers	Air	Dichloromethane and methanol, successively; Soak	0.00239	[55]
16	*Schisandra chinensis* (Turcz.) Baill.	Schisandraceae	Fruit Leaves	Lyophilizing Air	Methanol; Ultrasonic	0.2565 0.2717	[56]
17	*Caraipa densifolia* Mart.	Clusiacaeae	Fruit Leaves	Air	Hexane and methanol, successively; Soxhlet	0.74 0.11	[57]
18	*Citrullus colocynthis* (L.) Schrad.	Cucurbitaceae	Herbs	Air	Methanol; Soxhlet	0.0228	[58]
19	*Cucumis sativus* L.					0.097	
20	*Momordica charantia* L.					0.267	
21	*Paeonia suffruticosa* Andr.	Ranunculaceae	Petal Stamen Calyx Ovary	Lyophilizing	Hexane and 80 % methanol; Soak	0.4834 0.5311 0.5989 0.3896	[59]
22	*Achillea schischkinii* D.Sosn.	Asteraceae	Leaves	Air	Methanol; Soak	11.2	[60]
23	*Tinospora cordifolia* (Willd.) Hook.fil. & Thoms.	Menispermaceae	Stem	-	Methanol; Heating reflux	0.134	[61]
24	*Prunus spinosa* L.	Rosaceae	Fruit	Lyophilizing	Water; Soak	0.0411	[62]

25	*Mangifera indica* L.	Anacardiaceae				0.832	
26	*Fragaria* viridis (Duch.) Weston	Rosaceae			30 % Ethanol;	0.0311	
27	*Rubus idaeus* L.	Rosaceae				0.058	
28	*Vitis vinifera* L.	Vitaceae				0.0061	
29	*Malus domestica* Borkh.	Rosaceae	Fruit	⇳	Soak	0.0051	[63]
30	*Pyrus* L.	Rosaceae				0.112	
31	*Rhodiola crenulata* (Hook.f. & Thomson) H.Ohba	Crassulaceae	Root and Rhizome	⇳	Deionized water; Soak	8.1877	[64]

necrosis factor-α (TNF-α), nitric oxide (NO) and prostaglandin E2 (PGE2) [12,13]. Furthermore, immoderate inflammation may lead to diseases such as cardiovascular disease, septic shock, atherosclerosis, and immune dysfunction [14–16]. Therefore, anti-inflammatory therapy could be an optional to treat the diseases mentioned above [11]. Currently, non-steroidal anti-inflammatory drugs have a very definite effect in clinical practice, but the inevitable and serious side effects sometimes are fatal. Therefore, it is urgently needed to develop safe and effective anti-inflammatory drugs with fewer side effects [17]. Many studies have shown that traditional Chinese medicine (TCM) has a good effect on most diseases, with the advantages of relatively fewer side effects, lower price and easy access [18–20]. Among of which, GA has been demonstrated to exert mighty therapeutic effects on multifarious inflammation related diseases [21,22]. In the following statement, we will give a relatively comprehensive summary of its specific pharmacological mechanisms.

As far as the inflammatory cascade itself is concerned, nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) are even more crucial. Firstly, the activation of the inflammatory responses stimulated immune system is regulated by ubiquitously expressed NF-κB [23]. Subsequently, it causes a massive release of inflammatory cytokines, chemokines and adhesion molecules, which contributes to the pathological changes in organs or tissues, and results in intractable chronic inflammation [24,25]. In resting cells, NF-κB consisting of p50 and p65 heterodimers remains inactive by bounding to the inhibitory proteins of NF-κB (IκBs) in the cytoplasm. However, the activation and phosphorylation of IκB kinases (IκKs) in response to different stimuli, such as microbial pathogens, inflammatory cytokines, could ubiquitinate and degrade the IκBs proteasome. The degraded IκBs thus leads to the activation of NF-κB, which translocates to the nucleus and subsequently activates the target genes, such as IL-1β, TNF-α, thioredoxin-like protein 4B, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) [23,26,27]. Promisingly, it was announced that GA could block the expression of the above inflammatory mediators evoked by NF-κB [28]. Moreover, evidence indicated that GA could inhibit the secretion of pro-inflammatory mediators nitrite, NO, PGE2 and IL-6 in a dose-dependent manner with no significant effect on COX-2 production [29].

Secondly, varieties of inflammatory stimuli activated MAPK is a highly conservative signal transduction module. And it may participate in many cellular physiological/pathological processes

Fig. 1. The plant origins of GA. The pictures (except the sixth picture in the first row) are from the website: https://www.gbif.org/; http://www.iplant.cn/frps.

through MAPK kinase kinase (MKKK), MAPK kinase (MKK) or MAPK, respectively [30]. As a result, it could trigger inflammatory response in multiple diseases via extracellular signal-regulated kinases (ERK), C-Jun N-terminal kinases (JNK) and p38 [31,32]. In a classic MAPK signaling pathway, MKKK is primarily activated by pressure sensitive plasma membrane receptors, causing the secondary signal to be transmitted downstream. In details, MKKK phosphorylates and stimulates the conserved serine/threonine motif of MKK. Subsequently, MKK activates MAPK through simultaneous phosphorylation of both threonine and tyrosine [33,34]. Ultimately, MAPK activates downstream kinases, enzymes and transcription factors, which contributes to the information interaction across cell membranes [35–38]. So, it's not surprising that NF-κB and MAPK are viewed as two core targets in the inflammatory processes [39]. Furthermore, GA could also reduce inflammatory responses by regulating the TLR4/MyD88/TRIF signaling pathway [40,41]. Based on the robust anti-inflammatory effects of GA, we therefore have carried out a more comprehensive elaboration on the mechanisms of action, so as to lay a solid foundation for its clinical usage.

2. Chemical properties and various sources of GA

GA, with phenol and carboxylic acid properties, is an organic acid containing only one benzene ring structure. Its molecular formula is $C_7H_6O_5$ and has three adjacent − OH groups at the 3, 4, 5 positions, and one − COOH group at the 1 position. The pure GA are white or light brown needle-like crystals or powders with melting points of 235− 240 °C (decomposition). It is structurally unstable, losing crystal water when heated to 100− 120 °C and carbon dioxide when heated to more than 200 °C. And its solubility is as follows: boiling water > acetone > ethanol > glycerol > water (25 °C) > ether > benzene ≈ chloroform ≈ petroleum ether (Data on chemical properties were obtained from: https: //pubchem.ncbi.nlm.nih.gov/compound/370). Numerous studies have shown that GA extensively consists in the roots, stems, leaves, fruits, skins, flowers and seeds of many medicinal plants, such as *Phyllanthus A.* (Euphorbiaceae), *Momordica C.* (Cucurbitaceae), *Achillea S.* (Asteraceae), *Mentha S.* (Lamiaceae) and *Abutilon P.* (Malvaceae) [42–64]. However, the content of GA isolated from these medicinal plants varied greatly, ranging from 0.001–135.08 mg/g (Table 1). Among all the herbals (Fig. 1), the concentration of GA in *Phyllanthus A.* was the highest, followed by *Momordica C.* and *Achillea S.* (Table 1). This provides a reliable and effective reference for the extraction and enrichment of GA in large quantities. Pertinently, TCM defines inflammation as the defensive response of the body after being strongly stimulated by the external six excesses, characterized by redness, swelling, heat and pain [65]. As expected, we have sorted out that the most of herbs have the effect of clearing away heat and detoxifying and diuresis, which partially contributes to explain the anti-inflammatory effects of GA.

Table 2
Pharmacokinetics of GA *in vivo*.

Medicinal herbs/ prescriptions	Doses (g/kg)	Animal	Effects on pharmacokinetics of GA	
Pueraria lobata (Wild.) Ohwi	4.61	SD rats	T_{max}, C_{max}, AUC ↓ $T_{1/2}$, CL, VD↑	
Ardisia japonica (Thunb.) Bl	0.93	SD rats	T_{max}, C_{max}, AUC ↓ $T_{1/2}$, MRT ↑	
Changtai Granule (*Phellodendro Chinense* Schneid., *Sanguisorba officinalis* L., *Euphorbia humifusa* Willd., and *Polygonum hydropiper* Linn.)	10	SD rats	T_{max}, $T_{1/2}$, C_{max} AUC, CL, VD ↓	
Hedyotis diffusa Willd.	4.837	SD rats	T_{max}, $T_{1/2}$, CL, VD ↓ C_{max}, AUC, MRT ↑	[71]
Polygonum capitatum Buch-Ham. ex D. Don	0.06	SD rats	$T_{1/2}$, C_{max}, AUC, CL, VD ↓ T_{max} ↑	[72]
Polygonum L.	0.7	SD rats	T_{max} ↓ C_{max}, AUC, MRT ↑	[73]
Keishibukuryangan -ka- yokuinin (*Paeonia lactiflora* Pall., *Poria cocos* (Schw.) Wolf, *Cinnamomum cassia* Presl, *Paeonia suffruticosa* Andrews, *Prunus Persica* (L.) Batsch; *Coix lacryma- jobi var. ma-yuen* (Rom.Caill.) Stapf)	2	SD rats	T_{max}, $T_{1/2}$, C_{max}, AUC ↓	[74]
Guizhi Fuling capsules (*Paeonia lactiflora* Pall., *Poria cocos* (Schw.) Wolf, *Cinnamomum cassia* Presl, *Paeonia suffruticosa* Andrews, *Prunus Persica* (L.) Batsch)	2 capsules (2.2 mg/ capsule)	Healthy volunteers	C_{max}, AUC ↓ Tmax, T1/2, MRT ↑	[75]
Juglans mandshurica Maxim.	15	Wistar rats	T_{max}, $T_{1/2}$, C_{max}, AUC ↑	[76]
Saxifraga stolonifera Meerb.	5	Wistar rats	T_{max}, C_{max}, AUC ↓ $T_{1/2}$, MRT, CL, VD ↑	[77]
Mangguo ZhiKe tablets (*Mangifera indica* L.; Chlorpheniramine maleate)	0.4	SD rats	Tmax, T1/2, Cmax, AUC ↓ CL ↑	[78]
Rheum rhaponticum L.	5	SD rats	$T_{1/2}$ ↓ T_{max}, C_{max}, AUC, MRT ↑	[79]

3. Pharmacokinetics of GA

Favourable pharmacokinetic properties (PPs) are the premise of clinical application of drugs, such as the increasing popularity of peptide drugs [66]. A

thorough understanding of the PPs of medicines could help us comprehend the processes of its absorption, distribution, metabolism and excretion (ADME) processes in the body. Yu et al. comprehensively detected the following PPs of GA in SD rats: the mean time to peak concentration (T_{max}), maximum plasma concentration (C_{max}), terminal elimination half-life ($T_{1/2}$), plasma concentration time curve (AUC), mean residence time (MRT), clearance rate (CL) and volume distribution (VD). The specific values of these key parameters are 1.5 h, 0.83 μg/mL, 2.56 h, 0.137 mg min/mL, 2.67 h, 0.37 L/min/kg and 78.52 L/kg, respectively [67]. To analyze the pharmacokinetic differences of GA in acidum gallicum tablets and black tea (both containing 0.3 mM GA), Shahrzad et al. determined the PPs by HPLC analysis and found that the higher bioavailability of GA may be related to its lower absorption and elimination rates in black tea [68]. And Zhao et al. used HPLC/MS-MS analysis to compare the PPs of GA and GA-loaded carboxymethyl chitosan nanoparticles after gavage treatment in SD rats [69]. Compared with GA, the bioavailability of nano-preparation was improved due to the lower absorption and elimination rates. Well-known, PPs are influenced by many factors, such as gender, age, health status, drug form and dose, etc. A large number of studies have shown that the PPs of GA in medicinal herbals and some foods are evidently different from pure compounds, such as in *Pueraria L*. and black tea [42,68]. The PPs of GA in diverse herbs are shown in Table 2. Nevertheless, the mechanisms of different components on the pharmacokinetics of GA still remain unclear.

As mentioned above, pathological factors also influence the PPs of GA. Yu et al. exhibited that GA showed the characteristics of slower absorption and elimination, while wider distribution and bioavailability in myocardial infarction rats compared with the normal [80]. Zhu et al. further announced the similar changes as above statement in acute blood stasis rats after administration of rhubarb [79]. Latterly, the mechanisms of GA metabolism and excretion are also gradually emerging. The results showed that GA was speedy and universally distributed in all tissues, with the highest in the kidneys, followed by the heart, liver, spleen and lung [71]. However, Liu et al. found that GA was mainly distributed in the kidneys and liver, but not in other organs [42]. Both studies collectively revealed that the kidneys maybe the main metabolic organ of GA. What's more, identifying GA metabolites *in vivo* may shed light on its mechanisms of action or discover new and more potent natural products. GA has many metabolites with similar structures, such as 3-dihydroshikimic acid, ethyl gallate, syringic acid and pyrogallol. Interestingly, 3-dihydroshikimic acid could be converted to GA through the shikimic acid pathway, while GA could be metabolized to syringic acid by 3-O, 4-O and 5-O methylation [3,81]. Other studies also verified that GA has a variety of galloyl-glucose derivatives *in vivo*, such as 4-(3,4-dihydroxy-6-hydroxy hydroxymethyl-5-methoxy- tetrahydro-pyran-2-yloxy)-3-hydroxy-5-methoxy-benzoic acid and 1,3, 4,6-Tetra-O-galloyl-β-D-Glucose [81–83]. The GA related metabolites and their physicochemical properties were expounded in Fig. 2 and Table 3. In brief, GA is firstly absorbed by the gastrointestinal tract, then mainly distributed in the kidneys. And it is metabolized by the liver and excreted by the kidney, respectively. Noteworthily, methylation, glucoside acidification and sulfated products are the main forms of GA *in vivo*.

4. Toxicity of GA

The results manifested that 200 μM GA had no cytotoxic effect on HepG2 cells while was slightly cytotoxic to B16F10 and RAW 264.7 cells at concentrations higher than 200 μM [84–86]. It also has been shown that GA at the concentrations of 1.18 and 2.35 mM are a non-toxic state for RAW 264.7 cells [29,87]. However, Wu et al. demonstrated that GA could generate significant cytotoxicity in co-cultured RAW 264.7 and HEPA1–6 cells at concentrations over 25 μM [86]. Haute et al. found that 1000 μM GA had no effect on the cell viability of neutrophils [88]. The result showed that 5− 50 μM GA treatment had no effect on cell survival rate, however, higher concentrations of GA (≥100 μM) are toxic to BV-2 and Nerve-2A cells [89]. Truzzi et al. showed that 235.13 μM GA produced significant cytotoxicity on three different cell lines (Caco2, L929 and U937) [90]. They further illustrated that 117.57 μM GA was cytotoxic in a three-dimensional intestinal model consisting of mucosal layers, submucosal fibroblasts and monocytes. In addition, *in vivo* experiment had demonstrated that GA, at the dosage of 210 mg/kg, also had no toxic effects on BALB/c mice [91]. The acute toxicity of GA in albino mice showed that the LD_{50} of GA was greater than 2000 mg/kg. Coincidentally, a 28-day sub-acute toxicity study at a higher dosage of 900 mg/kg showed that GA did not alter the behavior, morphology and histopathological parameters of the mice [92]. ADMET properties of GA and relevant metabolites are exhibited in Fig. 3 and Table 3. These results indicated that GA is safe and effective for most cells at lower concentrations while toxic at relatively higher concentrations. Conformably, the toxicity of GA *in vivo* is relatively faint.

5. Pharmacological activities associated with antiinflammation of GA

5.1. Allergic inflammation

As a special pathological immune response, most of allergic inflammatory diseases (AIDs) have the traits of hyperblastosis, sclerosis and fibrosis. For allergens, pollens and air pollutants were proved to aggravate the accumulation of eosinophils in peripheral blood of individuals with AIDs [108]. As representative AIDs, allergic dermatitis, rhinitis, asthma, purpura and anaphylactic shock could affect the patient's daily life or even being life threatening [109]. Gratifyingly, GA has been shown to be involved in inflammatory and allergic diseases by regulating the intracellular MAPK and NF-κB pathways. GA inhibited the release of histamine by regulating intracellular cyclic adenosine monophosphate (cAMP) and Ca^{2+} levels. Further, it decreased the expression of inflammatory cytokines TNF-α and IL-6 via attenuating the activation of NF-κB and p38 MAPK. Eventually, GA mitigated the systemic or local allergic inflammatory reactions evoked by compound 48/80 or immunoglobulin E (IgE), respectively [44]. As a common allergic skin disease, atopic dermatitis is characterized by redness, swelling, dryness and thickening [110]. Liu et al. demonstrated that GA could inhibit p38 MAPK,

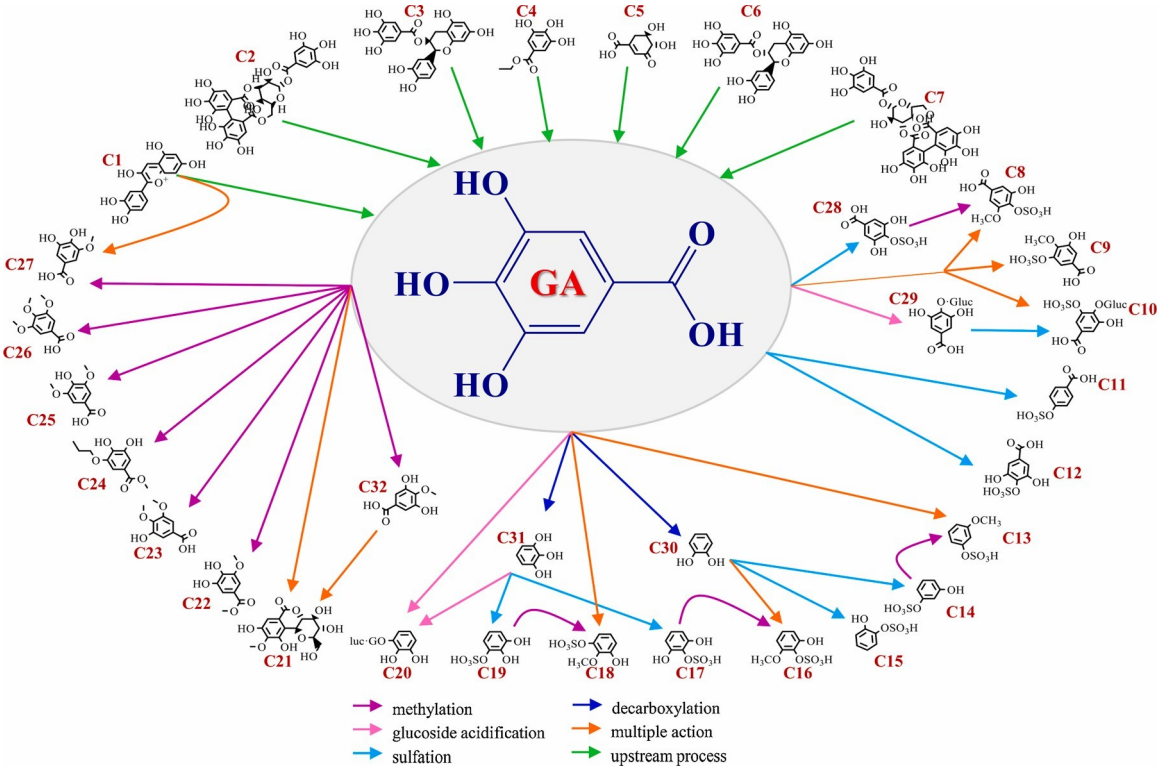

Fig. 2. The metabolites of GA in the plant. There are two results of GA metabolism in the body: inactivation, converting to non-pharmacological active compounds; activation, transforming into compounds which owns pharmacological activity or toxic, or retains its original pharmacological activity after metabolism. The compounds of C1-C7 are naturally present in plants and could be converted to GA through a series of metabolic processes *in vivo*. The compounds of C8-C32 are direct or indirect metabolites of GA through methylation, glucoside acidification and sulfation *in vivo*.

JNK and NF-κB in IL-33 induced KU812 cells. It thus reduced the release of intercellular adhesion molecule (ICAM-1), chemokines and inflammatory factors [111]. These results suggest that GA can effectively alleviate the symptoms of atopic dermatitis, partially associated with the regulation of MAPK and NF-κB pathways. Clearly, the characteristics of allergic rhinitis (AR) are nasal obstruction, rhinorrhea, sneezing and itching. Imbalance of type 1 helper T cells (Th1)/Th2 was considered to be a vital immune mechanism to increase the risk of AR by upregulation of Th17 cells [112]. While GA stimulated Th1 to release interferon gamma (IFN-γ) and IL-12, resulting in the inhibited secretion of IL-4/5/17 and retinoic-related orphan receptor gamma t (ROR-γt) transcription factors of Th2 and Th17 cells. Meanwhile, GA also reduced nasal mucosal thickness and goblet cell proliferation by suppressing the infiltration of eosinophils, evidenced by elevated IgE and IgG1 expressions. Parallelly, GA could weaken the OVA/IL-33 induced infiltration of inflammatory cells and the number of Group 2 lymphoid cells by inhibiting the expression of MyD88 and NF-κB p65 in the lung. And these contributed to alleviate the airway hyperresponsiveness in asthma, evidenced by downregulating Th2 cytokines-evoked IL-5/13/33 levels [113]. To sum up, GA can target MAPK, NF-κB and MyD88 to improve the symptoms of AIDs by alleviating inflammation related immune responses.

5.2. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by progressive destruction of cartilage and bone, as well symmetric multijoint swelling and pain [114]. Fibroblast-like

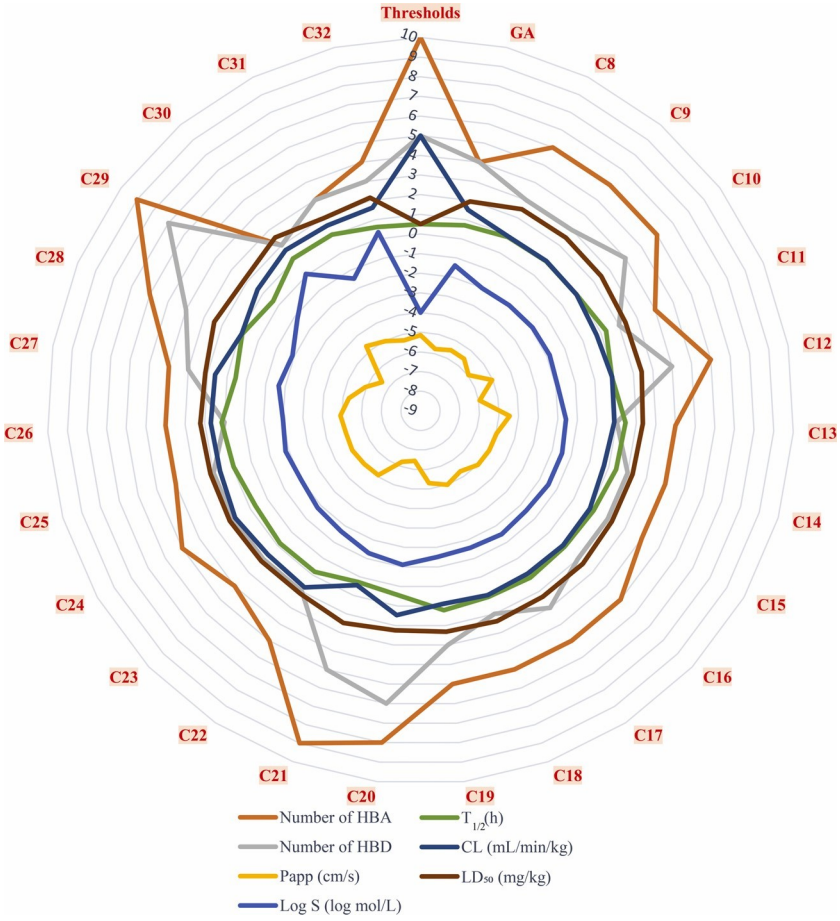

Fig. 3. Radar chart involved in ADMET properties of GA and relevant metabolites compared with the thresholds [93–99]. HBA, hydrogen bond accepter; HBD, hydrogen bond donor; Papp, apparent permeability coefficient; Log S, solubility; $T_{1/2}$, terminal elimination half-life; CL, clearance rate; LD_{50}, median lethal dose of acute toxicity. The optimal range of the above parameters: HBA, <10; HBD, <5; Papp, >-5.15 cm/s; Log S, >-4 log mol/L; $T_{1/2}$, >0.5 h; CL, <5 mL/min/kg; LD_{50}, > 0.373 -log mol/kg. The more the compound fits into the optimal range, the more likely it is to be developed as a new anti-inflammatory drug. The data are obtained from the website: http://admet.scbdd.com/#.

Table 3
Physicochemical properties and ADMET systematic evaluation results for GA and relevant metabolites [100–107].

Compounds	Mw	Log P	Number of HBA	Number of HBD	TPSA (A^2)	Log S (log mol/L)	Papp (cm/s)	HIA	F	VD (L/kg)	BBB	$T_{1/2}$ (h)	CL (mL/min/kg)	H-HT	LD_{50} (-log mol/kg)	DILI
GA	170.12	0.502	4	4	97.99	− 1.397	− 5.767	-	+	− 0.766	-	0.705	1.507	—	1.943	-
C8	264.211	0.281	6	3	130.36	− 2.017	− 5.542	-	+	− 1.078	—	0.898	0.931	-	2.484	-
C9	264.211	0.281	6	3	130.36	− 1.987	− 5.543	-	+	− 1.062	—	0.935	0.952	-	2.504	-
C10	250.184	− 0.022	6	4	141.36	− 1.893	− 5.96	-	+	− 0.997	—	0.903	0.898	—	2.466	-
C11	218.186	0.566	4	2	100.9	− 1.849	− 5.032	-	+	− 0.983	-	1.283	0.756	-	2.358	-
C12	250.184	0.022	6	4	141.36	− 1.903	− 5.944	-	+	− 0.999	—	0.886	0.905	—	2.429	-
C13	204.203	0.877	4	1	72.83	− 1.585	− 4.456	+	+	− 0.712	+++	1.45	0.88	-	2.331	-
C14	190.176	0.574	4	2	83.83	− 1.48	− 4.958	-	-	− 0.78	+	1.39	0.74	-	2.263	-
C15	190.176	0.574	4	2	83.83	− 1.493	− 4.96	-	+	− 0.776	++	1.165	0.957	—	2.247	-
C16	220.202	0.582	5	2	93.06	− 1.606	− 4.995	-	+	− 0.749	++	1.076	0.974	-	2.351	-
C17	206.175	0.279	5	3	104.06	− 1.484	− 5.308	-	+	− 0.765	+	1.161	0.913	-	2.319	-
C18	220.202	0.582	5	2	93.06	− 1.577	− 4.995	-	++	− 0.727	++	1.076	0.978	-	2.39	-
C19	206.175	0.279	5	3	104.06	− 1.516	− 5.3	-	+	− 0.761	++	1.215	0.885	-	2.317	-
C20	288.252	− 1.724	8	6	139.84	− 1.111	− 6.429	—	—	− 1.078	+	0.455	1.47	-	2.242	—
C21	328.273	− 1.201	9	5	145.91	− 1.287	− 6.242	—	-	− 1.209	-	0.272	0.445	-	2.491	—
C22	198.174	0.893	5	2	75.99	− 1.655	− 5.081	+	+	− 0.752	++	0.801	1.749	-	2.135	—
C23	198.174	1.108	4	2	75.99	− 1.805	− 5.058	+	+	− 0.734	—	0.827	1.666	—	2.142	—
C24	226.228	1.673	5	2	75.99	− 1.99	− 4.984	+	+	− 0.631	+++	0.691	1.9	-	2.203	—
C25	198.174	1.108	4	2	75.99	− 1.83	− 5.049	+	+	− 0.75	+	0.927	1.648	-	2.165	—

C26	212.201	1.411	4	1	64.99	− 1.985	− 4.916	+	++	− 0.636	++	1.139	1.692	—	2.226	—
C27	184.147	0.805	4	3	86.99	− 1.669	− 5.297	+	+	− 0.748	-	0.559	1.61	-	2.12	—
C28	250.184	0.022	6	4	141.36	− 1.903	− 5.944	-	+	− 0.999	—	0.886	0.905	—	2.429	—
C29	332.261	2.025	9	7	177.14	− 1.19	− 6.564	—	—	− 1.316	—	0.352	1.335	—	2.175	—
C30	110.112	0.803	3	4	60.69	0.086	− 5.033	+	+	− 0.245	+++	1.11	1.678	—	2.515	—
C31	126.111	0.805	3	3	86.99	− 1.466	− 5.313	+	++	− 0.545	+++	1.036	1.558	—	1.974	—
C32	184.147	1.098	2	2	40.46	0.341	− 4.704	+	+	0.808	—	0.612	1.625	—	2.146	—

BBB, blood–brain barrier; DILI, drug induced liver injury; F, 30 % bioavailability; HIA, human intestinal absorption; H-HT, human hepatotoxicity; Log P, distribution coefficient P, optimal: 0 < Log P < 3; Mw, molecular weight; TPSA, topological polar surface area; VD, volume distribution, optimal: 0.04− 20 L/kg. The data are obtained from the website: http://admet.scbdd.com/#.

synovial cells (FLSs) within the synovial tissues are the point to maintain synovial inflammation and progressive joint destruction [115]. Recent studies have shown that tumor-like FLSs cells could migrate to cartilage and bone, resulting in the formation of pannus via accelerating the secretion of pro-inflammatory cytokines, chemokines and matrix metalloproteinases (MMPs) [116–119]. Surprisingly, it was testified that GA could trigger the apoptosis of FLSs by promoting the expression of pro-apoptotic Caspase-3, Bax and p53 proteins, while inhibiting the expression of anti-apoptotic Bcl-2 and p-AKT proteins. Consequently, the inflammatory response was ameliorated by lessening the release of IL-6, CCL-2/7, COX-2 and MMP-9 [120]. As an important "energy sensor" of AMP/ATP, AMP-activated protein kinase (AMPK) could regulate intracellular metabolism and energy balance [121]. The activated AMPK was demonstrated to increase the expression of deacetylase-dependent silencing information regulator 1 (SIRT1) by elevated NAD^+ concentration, thus inhibiting the increase of NF-κB [122,123]. Evidences had shown that GA could improve the level of cAMP by selectively inhibiting the activity of phosphodiesterase 4 (PDE4), which contributed to the improvement of local RA inflammatory response [124]. Accordingly, we proposed that GA could stimulate cAMP triggered AMPK/SIRT1/NF-κB signaling pathway by suppressing the activity of PDE. It was well known that the pathogenesis of RA tended to be similar to cancer in some aspects, such as malignant proliferation, while GA can effectively combat the aberrant proliferation [120,125,126]. Given its robust anti-inflammatory activities and superior inhibitory effect on malignant proliferation of FLSs, GA could be used as a candidate drug for RA treatment.

5.3. Colitis

Inflammatory bowel disease (IBD) includes at least two forms of intestinal inflammation: Crohn's disease and ulcerative colitis (UC) [127]. UC is characterized by abdominal pain, hematochezia, mucosal ulceration and recurrent diarrhea [128]. Recently, the imbalance between pro-inflammatory and anti-inflammatory cytokines have attracted intensive attentions as the pathogenesis of UC [129]. As a marker of neutrophil infiltration, Pandurangan et al. showed that GA lowered the expression of myeloperoxidase (MPO) by restraining the IL-6/STAT-3 and IκB/NF-κB signaling pathways in dextran sodiumsulfate induced experimental UC [130]. GA refrained the expression of pro-inflammatory cytokines IL-1/6, TGF-β and TNF-α, as well stimulated the release of anti-inflammatory cytokines IL-4/10 by inhibiting the IκB/NF-κB pathway [131]. By suppressing NF-κB signaling pathway, causing the decline of pro-inflammatory factors COX-2 and iNOS, GA could reverse UC induced by 1, 2-dimethylhydrazine [132]. To sum up, GA may be involved in the pathogenesis of UC mainly through the regulation of the NF-κB signaling pathway, but more experimental data are needed to support this view.

5.4. Pneumonia and hepatitis

Evidence have showed that chronic obstructive pulmonary disease (COPD) could induce pneumonia, which elicit small airway obstruction (chronic bronchitis) and parenchymal destruction (emphysema) [133, 134]. Singla et al. confirmed that GA effectively ameliorated pulmonary inflammation and emphysema of mice COPD partly by inhibiting the IκB/NF-κB signaling pathway [135]. In addition to its mighty anti-oxidant effect, GA also reduced the amounts of COX-2 and TNF-α by inhibiting the NF-κB pathway [136,137]. In a co-culture of lipid-laden Hepa 1–6 hepatocytes and RAW 264.7 macrophages, GA reduced the expression of TNF-α and IL-1β [86]. According to the above analysis, the potential effects of GA observed in these studies could be effective in preventing nonalcoholic steatohepatitis and its complications.

5.5. Pelvic inflammation and gastroenteritis

Pelvic inflammatory disease is the most common disease caused by pathogens of female upper reproductive tract, mainly including endometritis, salpingitis, salpingo-ovaritis, pelvic peritonitis and other diseases [138]. PID could induce diffuse peritonitis, sepsis, septic shock and in severe cases, life threatening [139]. Gastroenteritis is often caused by unclean diet, medicine and accidental taking of toxic substances, etc [140]. Its similarity is diarrhea with collective morbidity or frequent occurrence in the family. Generally speaking, the etiology could be divided into food, water and other causes. Feiyang Changweiyan capsule (FYC), a traditional Chinese patent medicine mainly containing GA, was extensively used to treat bacterial dysentery and acute or chronic gastroenteritis [91,141]. GA could significantly improve the uterine enlargement, bleeding and suppuration, and reduce the infiltration of the polymorphonuclear cells by inhibiting the IκB/NF-κB pathway in uterine tissue [142]. Study has shown that GA also has a significant protective effect against alcohol-induced gastric ulcers by reducing cell infiltration and submucosal edema in a dose-dependent manner via inhibiting the release of IL-1β/6 and TNF-α [143]. From the above results, GA could effectively treat the diseases mentioned above, which may be mainly through the regulation of NF-κB signaling pathway, and we may be able to focus on this aspect in future research.

5.6. Obesity

Obesity was well known to cause chronic inflammation, which leading to metabolic diseases, including insulin resistance, type 2 diabetes, cardiovascular diseases and many types of cancer [144]. Adipose tissue inflammation was caused by adipocyte hypertrophy and paracrine interaction between adipocytes and infiltrating macrophages [145]. GA restrained the activation of macrophages induced by adipocyte hypertrophy and down-regulates the expression of inflammatory mediators, thus playing a key role in improving obesity of the body [86]. Advanced glycation end products (AGEs) referred to the products formed by condensation, rearrangement and other effects of free amino groups of proteins, amino acids and other large molecules under non-enzyme-catalyzed conditions [146]. Study had shown that AGEs induced systemic inflammation in mice, subsequently leading to weight gain. While GA could suppress the AGEs expression by lowering the levels of inflammatory cytokines IL-1β/16, ICAM-1, TIMP-1 and C5a, and chemokines BLC, SDF-1 and CCL-2 [147]. Although studies have shown that GA can effectively improve inflammation-related obesity, the specific mechanisms of action have unfortunately not been reported, which may serve as a focus for our future attention.

5.7. Other inflammation-related diseases

Moreover, the anti-inflammatory effects of GA also help improve neurodegenerative diseases, diabetic retinopathy, thyroid dysfunction and cancer. As a histone acetyltransferase inhibitor, GA could counteract amyloid-induced neurotoxicity by selectively suppressing NF-κB activation in the animal model of Alzheimer's disease [89]. Furthermore, Liu et al. indicated that GA could recede α-nucleoprotein, GFAP and ED-1 proteins, resulting in suppressed IL-1, NO and iNOS levels in LPS-simulated Parkinson's disease [148]. As the main pathological manifestation, GA has exerted its anti-retinal angiogenesis by inhibiting the phosphorylation of p38, ERK and NF-κB, as well lowering the expression of inflammatory cytokines IL-6/8 and chemokine CCL-2 [149]. Evidences have revealed that inflammatory cascades could result in thyroid dysfunction [150,151], while Mohamed has shown that GA could be used to improve thyroid dysfunction in potassium dichromate induced inflammation of albino rats [152]. The involved mechanisms may be related to increase the serum levels of free FT3 and FT4, while down-regulate the expressions of NO, iNOS, TNF-α, IL-6 and COX-2 levels in the thyroid [152]. Studies also have shown that GA can inhibit the secretion of MMP-2/9 and migration of gastric adenocarcinoma cells by inhibiting the activities of IκB/NF-κB and PI3K/AKT signaling pathways [153,154]. Coincidentally, inhibition of p300/CBP mediated p65 acetylation and subsequent IκB/NF-κB signal activation could reduce the expression of inflammatory mediators in A549 lung cancer cells. Beyond that, it also inhibited NF-κB-evoked expression of antiapoptotic and cell survival genes, such as XIAP, Bcl-2, cyclin D1 and c-Myc [155]. In accordance with the above analyses, García-Rivera showed that GA could regulate IκK/IκB/NF-κB, MAPK and MEK1/p90RSK/MSK signaling pathways in MDA-MB231 breast cancer cells [156]. Consequently, it reduced the expression of downstream target genes of inflammation, metastasis and anti-apoptosis, such as IL-6/8, COX2, CXCR4, XIAP and Bcl-2 [156]. Given its powerful pharmacological properties, GA, to some extent, could be indeed a potential anti-inflammatory candidate by inhibiting the NF-κB and MAPK signaling pathways.

6. Discussion and future prospects

In recent decades, TCM has become an important source of new drug development [157], attracting widespread attention for their clear efficacy, low toxicity and affordable prices, such as paclitaxel and artemisinin [158,159]. As mentioned

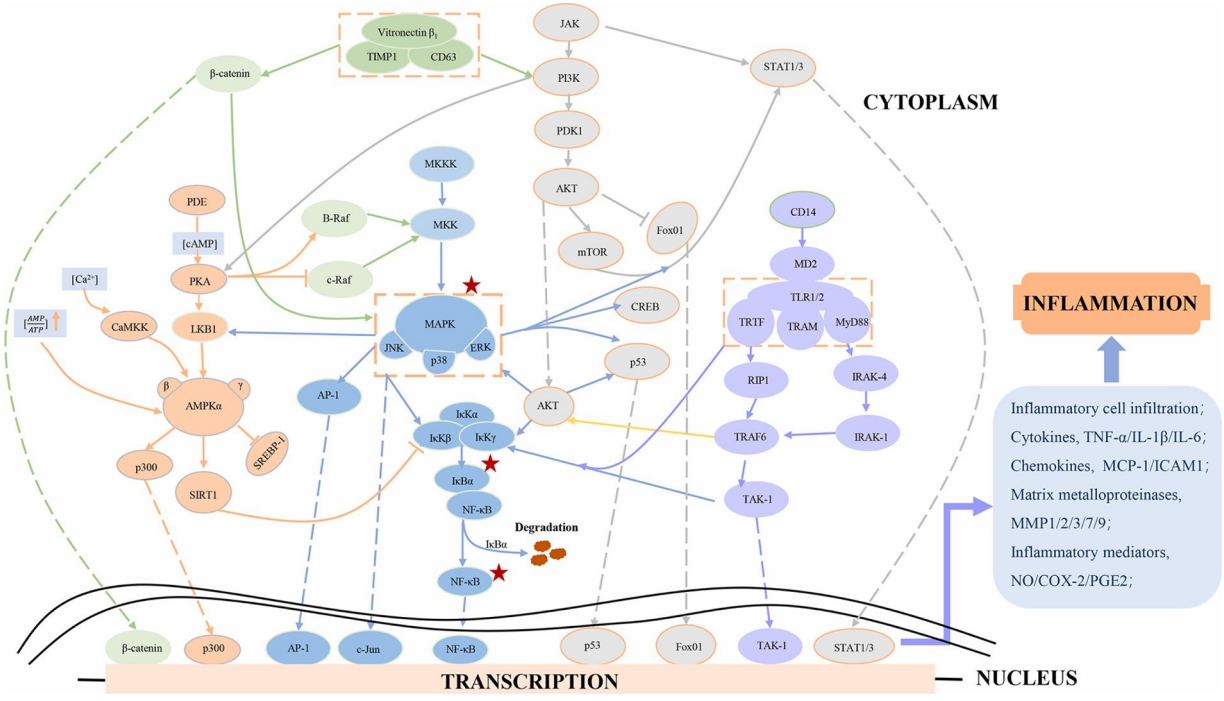

Fig. 4. Schematic summary of the major signaling pathways and possible molecular mechanisms modulated by GA. Different modules indicate different targets of the GA's anti-inflammatory properties. Blue modules, MAPK and NF-κB pathways; Gray module, PI3K/AKT pathway; Green module, MMPs pathway; Orange module, AMPK pathway; Purple module, TLRs pathway. Blue modules are the main mechanisms of GA and the others are the potential targets. Red pentacles, the key targets of GA; Full lines denote for direct interaction between proteins; Imaginary lines stand for protein translocation.

earlier, GA, as a natural plant secondary metabolite, has been proven to exert an anti-inflammatory role in neurodegenerative diseases, metabolic diseases, arthritis, cancer and other pathological conditions. This paper reviewed the chemical properties, plant origins, ADMET properties and pharmacodynamic mechanisms of GA. Compared with the commonly used anti-inflammatory drugs in clinical practice, GA not only has fewer side effects, but significantly strengthens the immunologic function of the body as well. And more importantly, it has obvious advantages of multi-action targets. Common targeted anti-inflammatory agents are effective, but they are also prone to side effects and adverse reactions such as liver and kidney damage of aspirin and gastrointestinal reaction of amoxicillin [160,161]. However, from our review, GA has hardly shown toxicity in animals or clinical trials, thus making it potentially useful for long-term use in inflammation-related diseases. In addition to its predominant anti-inflammatory effects, GA can also reduce the incidence of inflammation-related diseases through anti-oxidative stress, anti-apoptosis and anti-viral mechanisms [1,162–164]. The data collected in this paper will be of certain reference value to the research and development of GA in the future.

GA itself is characterized by poor stability and low bioavailability [165]. Therefore, although GA has a beneficial effect in improving inflammation, the above disadvantages may limit its therapeutic applications. As a phenolic acid compound with a simpler structure, GA contains only one benzene ring structure. So optimizing its structure or adjusting its dosage form are good choices to change its physicochemical and ADMET properties. Therefore, Nabavi et al. methylated the carboxyl group and the hydroxyl group on the 3-position of GA to obtain its derivative M3OMG, showing better anti-inflammatory pharmacological activities than GA [3]. The introduction of methyl groups could increase the lipophilicity and absorption of GA, resulting in a stronger anti-inflammatory activity. However, further lipophilic modification of M3OMG to the propyl derivative (P 3OMG) does not correspond to an increase in activity. This indicates the importance of selecting appropriate sites or small molecular groups for structural optimization. In addition, using nanotechnology to improve the common dosage forms of GA could improve the bioavailability of GA and adjust its physicochemical properties. Nano-GA was accomplished by double emulsification and solvent evaporation with Eudragit RS 100 polymer and polyvinyl alcohol as carriers. By comparing the effects of nano-GA and pure GA, it was found that nano-GA suppressed the release of IL-6, TNF-α and other inflammatory factors significantly better than pure GA [166]. In addition to increasing its bioavailability by modifying the dosage form, studies have shown that combining GA with other drugs could also increase its medicinal efficacy. It was demonstrated that the combination of GA with leucine by artificial synthesis could obtain a new compound GA-L-leucine (GAL) conjugate and increase its activity [167]. This unconventional compound plays an anti-inflammatory role by attenuating the activation of MAPK and NF-κB/AP-1 signaling pathways, which reduces the expression of inflammatory factors and related enzymes. Those indicate that reasonable structural modification of GA could optimize its PPs and enhance anti-inflammatory properties. We analyzed the existing tissue distribution data and found that GA was mainly distributed in the small intestine, followed by the kidneys and liver [26,42,168], proposing a stronger anti-gastroenteritis effect. Indeed, some studies have shown that authorized prescription FYC, with GA as the main medicinal ingredient, can effectively treat gastroenteritis caused by various reasons [91]. According to the literature we consulted, only a few articles reported the distribution of GA *in vivo*, which may limit our understanding of GA to a certain extent. In future studies, we may use UPLC-MS/MS, confocal imaging and fluorescence *in vivo* imaging to make up for the deficiency in the study of GA tissue distribution.

As mentioned above, GA comes from a wide range of sources and could be found in most fruits and plants. Nevertheless, how to improve the extraction rate of GA to meet the current market demand is also another problem worth thinking about. We thus compared the methods and results of GA extraction with the same plant by two different groups [49,58]. One group extracted the leaves from fresh plants by soaking them in distilled water and oscillating them evenly, while the other group used plants that had been stored for a period of time, using a Soxhlet extractor as an extraction tool and methanol as a solvent. The GA extraction rate of the former was significantly higher than that of the latter. This indicates that using aqueous solution as extraction solvent, accompanied by artificial or instrumental stirring at intervals, may be a wise choice to improve the extraction rate of GA. In addition to the most direct way of extracting GA from plants, we may also obtain large amounts of GA through artificial synthesis to fill up the market demand for it. For example, GA is obtained by demethylation of gallate methyl ester [169].

Thematically, we analyzed the main mechanisms of the anti- inflammatory effects of GA and found that these were mainly accomplished through the classic NF-κB and MAPK signaling pathways. GA inhibits the activities of NF-κB and MAPK, subsequently inhibiting the release of inflammatory factors (TNF-α, IL-1β/6), chemokines (CCL-2, ICAM-1, TIMP-1) and other inflammatory mediators such as COX-2 and NO. It also decreases inflammatory cell infiltration, thereby ameliorating the inflammatory response. From the perspective of current research, the action mechanisms of GA are mainly focused on the two signaling pathways mentioned above, which may restrict the exploitation and utilization of GA. Hence, to find potential targets or pathways of GA is another problem that needs to be solved urgently. TLRs signaling pathway and inflammasome are also known to be involved in inflammatory processes [170,171], while the current studies have not paid attention to either, which may deserve our attention in the future. As we all know, cancer and atherosclerosis are thought widely to be closely related to inflammation [172,173]. Research had shown that MyD88 could regulate NF-κB/MAPK signaling pathway, thus infuriating the migration and invasion of LPS-induced colorectal cancer cells by inflammation amplification [174]. Furthermore, Echizen proposed that targeting the COX-2/PGE2

and TLRs/MyD88 signaling pathways could be an effective preventive or therapeutic strategy for gastric cancer [175]. Interestingly, Xie et al. verified that atherosclerosis can be improved by modulating TLRs/MyD88/NF-κB [176]. And Koushki et al. seemed to confirm this view, they also stressed that NLRP 3 inflammasome was another important pathway in this disease [177]. Therefore, the above inflammatory signaling pathways may also be potential targets of GA in the treatment of inflammation-related diseases. Based on these, we summarize the main signaling pathways and potential molecular mechanisms of GA in anti-inflammatory effect in Fig. 4. Although many studies have demonstrated the anti-inflammatory activities of GA, inflammatory models constructed *in vivo* or *in vitro* cannot realistically simulate the real pathological state. These models only involved one organ lesion, however, the models of inflammation related multiple organs, such as brain metastasis of lung cancer and hepatic encephalopathy, cannot be completed by conventional methods. At present, microfluidic chip (MC) combined with multiple biosensors, mass spectrometry and automatic imaging systems has become a new platform for building multi-dimensional cell and organ models [178–180]. The model constructed by MC could more accurately simulate the pathological changes of living organisms, which may be a potential technical means for the establishment of multi-organ inflammation models in the future. In conclusion, the robust anti-inflammatory activities of GA could be used to treat a variety of inflammation-related diseases.

Author contributions

Xiaobo Wang and Xianli Meng conceived the study. Ce Tang, Ya Hou, Xiaopeng Ai, Xiaorui Chen and Yi Zhang reviewed and summarized the literatures. Jinrong Bai wrote the manuscript. Jinrong Bai, Yunsen Zhang and Xiaobo Wang drew all the figures. Xiaobo Wang and Xianli Meng supervised the study and gave final approval of the version to be published. The final version of the manuscript was read and approved by all authors.

Declaration of Competing Interest

The authors report no declarations of interest.

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